Dock t No. 68920-A/JPW/GJG/JBC

Application
for
United States Letters Patent

To all whom it may concern:

Be it known that

Daniella Licht, Suher Abd-Elhai, Rachel Cohen, Mazzi Dagan-Lion, Adrian Gilbert, Noa Leibovitch, Sasson Cohen and Ruth Levy

have invented certain new and useful improvements in

IMMEDIATE RELEASE FORMULATION OF N-(2-PROPYLPENTANOYL)GLYCINAMIDE

of which the following is a full, clear and exact description.

IMMEDIATE RELEASE FORMULATION OF N-(2-PROPYLPENTANOYL)GLYCINAMIDE

This application claims the benefit of U.S. Provisional Application No. 60/445,327, filed February 5, 2003, the entire contents of which are hereby incorporated by reference.

Throughout this application, various publications are referenced by full citations. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art as known to those skilled therein as of the date of the invention described and claimed herein.

Background of the Invention

Pain is considered to play a basic physiological role in the detection and localization of tissue damage or potentially damaging physiological processes. Pain has been broadly classified as somatogenic, where a physiological explanation can be found, or psychogenic, where the physiological explanation is not known (The Merck Manual of Diagnosis and Therapy, 16th Ed., pp. 1407-1426; PCT International Publication No. WO 02/13766 A2). An example of somatogenic pain is neuropathic pain.

Neuropathic pain is a category of pain, which includes several forms of non-nociceptive chronic pain, which result from dysfunction of nervous rather than somatic tissue. The majority of non-nociceptive chronic pains, in terms of either syndromes or cases, follow at various times after damage to either central or peripheral nervous tissue. Diagnosis of most of these syndromes and cases reveals a

dependence on abnormal spatial and temporal summation of natural somatic stimulation in the spinal cord and independence from somatic disease and peripheral sympathetic nervous system activity. The scientific pain research community defines this kind of pain as centrally mediated neuropathic pain and recognizes mechanistic, diagnostic, and therapeutic commonalities among pains of this class and differences between these and other syndromes.

Neuropathic pain can be defined as pain deriving from damage to or inflammation of central or peripheral nervous system tissue. Examples of pain syndromes of this class include post herpetic neuralgia, neuritis, temporomandibular disorder, myofascial pain, back pain, and pain induced by inflammatory conditions. Neuropathic pain may occur in all body regions. For example, the pain may originate from the dental region.

Burn injury also often leads to neuropathic hyperalgesia in the affected body area. Neuralgia is characterized, in its acute phase, by intraneural inflammation, which can cause damage to primary afferent axons, thus inducing neuropathic pain. Neuropathic pain may also be induced by diabetic conditions (diabetic neuropathy). Neuropathy of primary afferent axons in long nerves is found in diabetic patients. Nociceptor sensitization may ensue (U.S. Patent No. 6,054,461).

Pain can be both chronic and acute, and can also be evoked by noxious stimuli, also referred to as hyperalgesia, or by non-noxious stimuli referred to as allodynia (Attal, N. "Mechanism of action and rationale for use of antiepileptic drugs" (1999) in International Congress and Symposium Series 241 The Royal Society of Medicine Press, Limited Ed. JM

Pellock). Allodynia and hyperalgesia can have mechanical causes (dynamic or static), or a thermal cause. Examples of neuropathic pain include all the painful peripheral neuropathies and specifically diabetic peripheral neuropathy, postherpetic neuralgia, and trigeminal neuralgia. Trigeminal neuralgia, for example, is the most common neuralgic syndrome in the elderly. Other types of somatogenic pain that may have neuropathic components include cancer pain, postoperative pain, lower back pain, complex regional pain syndrome, phantom pain, HIV pain, arthritis (osteo-arthritis and rheumatoid arthritis) pain and migraines.

Pain may also be a symptom of headache disorders. Migraines constitute one of the four major categories of primary headaches (International Headache Society, 1988; Silberstein, S.D. et al. Headache in Clinical Practice, (1998) Pub. Isis Medical Media, Oxford). The other three types of primary headaches are tension -type, cluster and a miscellaneous-type (Id.). One current view is that there is a continuous spectrum of headache severity ranging from mild tension headaches to severe migraines. Others consider tension headaches and migraines to be distinct entities.

Neuropathic pain conditions are characterized by hyperesthesia (enhanced sensitivity to a natural stimulus), hyperalgesia (abnormal sensitivity to pain), allodynia (widespread tenderness, characterized by hypersensitivity to tactile stimuli), and/or spontaneous burning pain. In humans, neuropathic pain tends to be chronic. Consequently, alternate therapies for the management of this form of chronic or neuropathic pain are widely sought. (U.S. Patent No. 6,054,461).

The initial drug of choice for treating trigeminal neuralgia is carbamazepine. For other types of pain, such as postherpetic neuralgia and painful diabetic neuropathy, amitriptyline is most commonly used.

Drugs used in the treatment of headache disorders such as migraines originate from a broad range of different drug categories. These include: 5-hydroxytryptamine agonists (5-HT_1 agonists), dihydroergotamine, ergotamine, anti-emetics, anxiolytics, non-steroidal anti-inflammatory drugs, steroids, major tranquilizers, narcotics, beta-blockers, calcium channel blockers, anti-depressants, and anti-epileptic drugs. However, not all of the drugs in these categories are truly effective. While there are some drugs which are effective, there is still a need for more efficacious drugs, as well as a need for antimigraine treatments with fewer side effects.

As neuropathic pain tends to be chronic, drug treatment needs to be administered several times daily. The same is true for treating epilepsy. Epilepsy is an ancient disease, which affects about 1% of the global population. Despite the progress made in antiepileptic drug therapy, there are still many patients who continue to suffer from uncontrolled seizures and medication toxicity. At present, only the following 4 major antiepileptic drugs are in use: phenobarbital, phenytoin, carbamazepine and valproic acid. About 25% of the patient population is not seizure-free while treated with these medications (both mono and polytherapy), even when diagnosis and therapy is optimal ("Sustained Release Formulations of Antiepileptics" *Clin. Pharmacokinet.* (1992) 22(1): 11-24).

Major current antiepileptic drugs

Drug	Introduction (US Market)
Phenobarbital	1912
Phenytoin	1938
Carbamazepine	1968
Valporate	1978

In addition, uncontrolled epilepsy is a significant problem, as approximately 20% of patients do not respond to traditional therapies.

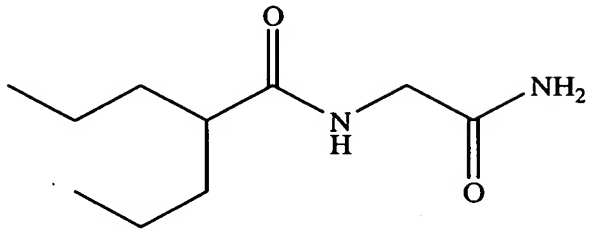
Valproic acid (VPA) is an anticonvulsant in both its spectrum of activity (tonic, atonic and myoclonic seizures, atypical absence) and its chemical structure. However, its chemical structure is unrelated to the structural features common in other anticonvulsants.

The basis of valproic acid's anticonvulsant activity has not been unequivocally determined. However, it is believed to be related to its ability to block sodium channels and to increase GABA concentration in the brain by enhancing GABA release from GABA-ergic neurons and inhibiting its metabolism.

VPA therapy has been associated with several side effects, of which the most common are GI side effects, pancreatitis, weight gain, hepatoxicity and teratogenicity.

Bialer, et al. (US Patent No. 5,585,358) disclose derivatives of Valproic acid amides and 2-Valpronoic acid amides, methods of making and pharmaceutical compositions comprising these compounds. The compositions are disclosed in tablet, suppository and solution forms, but the details of the manufacturing process are not disclosed.

N-(2-Propylpentanoyl)glycinamide is an anti-epilepsy and anti-pain drug which has the structure:



and can be prepared as disclosed by Bialer et al. in U.S. Patent 5,585,358. U.S. Patent 5,585,358 also describes a series of derivatives of valproic acid amides and 2-valproenic acid amides for the treatment of epilepsy and other neurological disorders.

Bialer et al. refer to the above compound as N-(2-n-Propylpentanoyl)glycinamide. However, in the present application, the compound is referred to as N-(2-Propylpentanoyl)glycinamide.

Published U.S. Patent Application No. US-2002-0052418-A1 discloses the use of N-(2-Propylpentanoyl)glycinamide and other derivatives of valproic acid amides and 2-valproenic acid amides for the treatment or prevention of pain and/or headache disorders.

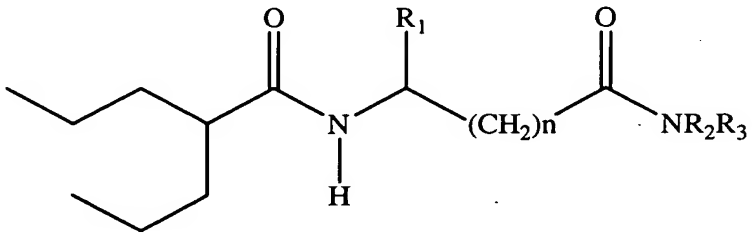
The present invention provides an immediate release pharmaceutical composition comprising the active-material N-(2-propylpentanoyl)glycinamide and a method of manufacturing the composition wherein the composition contains a large dose of the active material.

Summary of Invention

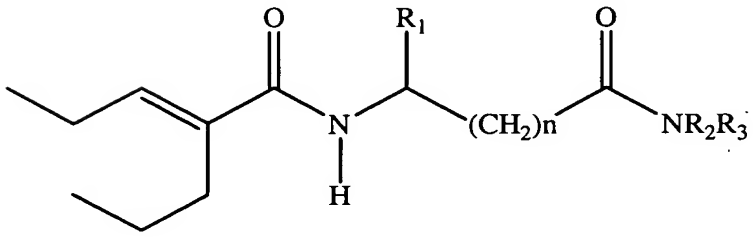
The subject invention provides an immediate release solid dosage form comprising the following components:

a) a uniform admixture of:

(i) an active ingredient selected from the group consisting of valproic sodium acid, a pharmaceutically acceptable salt or ester of valproic acid, divalproex sodium, valpromide and a compound having the structure:



or



wherein R_1, R_2, and R_3 are independently the same or different and are hydrogen, a C_1-C_6 alkyl group, an aralkyl group, or an aryl group, and n is an integer which is greater than or equal to 0 and less than or equal to 3; and

(ii) a hydroxypropyl cellulose, and

b) a disintegrant.

The subject invention also provides an immediate release tablet comprising the following components:

a) a uniform admixture of:

(i) N-(2-Propylpentanoyl)glycinamide; and

(ii) a hydroxypropyl cellulose; and

b) a disintegrant.

Detailed Description of the Figures

Figure 1 shows Mean plasma (SD) concentration of N-(2-propylpentanoyl) glycinamide after single oral administration of 1500 mg (3 x 500 mg) N-(2-propylpentanoyl) glycinamide under fasting or fed conditions.

-■- fasting state

-Δ- fed state

Figure 2 shows mean plasma (SD) concentration of N-(2-propylpentanoyl) glycine after single oral administration of 1500 mg (3 x 500 mg) N-(2-propylpentanoyl) glycinamide under fasting or fed conditions.

-■- fasting state

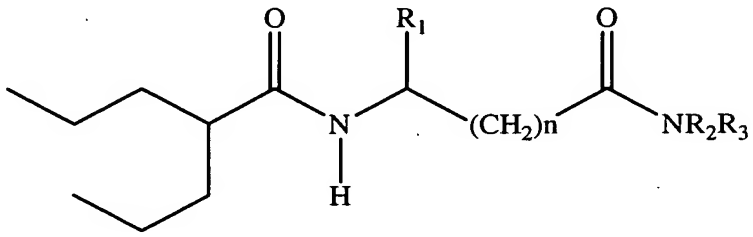
-Δ- fed state

Detailed Description

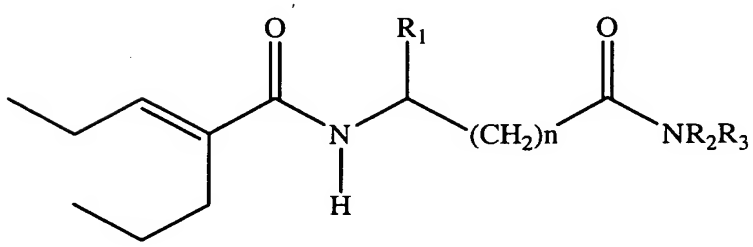
The subject invention provides an immediate release solid dosage form comprising the following components:

a) a uniform admixture of:

(i) an active ingredient selected from the group consisting of valproic sodium acid, a pharmaceutically acceptable salt or ester of valproic acid, divalproex sodium, valpromide and a compound having the structure:



or



wherein R_1, R_2, and R_3 are independently the same or different and are hydrogen, a C_1-C_6 alkyl group, an aralkyl group, or an aryl group, and n is an integer which is greater than or equal to 0 and less than or equal to 3; and

(ii) a hydroxypropyl cellulose, and

b) a disintegrant.

In one embodiment, the solid dosage form is a tablet.

In one embodiment, the uniform admixture of component a) further comprises a filler.

In another embodiment, the solid dosage form further comprises a filler and a lubricant as additional components.

In a further embodiment, the filler of component a) is a microcrystalline cellulose, lactose, a starch, or a combination of two or more of the foregoing.

In a further embodiment, the filler of component a) is a microcrystalline cellulose.

In a further embodiment, the additional filler is a microcrystalline cellulose, lactose, a starch, or a combination of two or more of the foregoing.

In a further embodiment, the additional filler is a microcrystalline cellulose.

In a further embodiment, the additional filler is lactose.

In another embodiment, the lubricant is magnesium stearate, sodium stearyl fumarate, hydrogenated castor oil, hydrogenated soybean oil, polyethylene glycol or a combination of two or more of the foregoing.

In a further embodiment, the lubricant is magnesium stearate.

In another embodiment, the lubricant is sodium stearyl fumarate.

In another embodiment, the disintegrant of component b) is croscarmellose sodium, sodium starch glycolate or a combination thereof.

In a further embodiment, the disintegrant of component b) is croscarmellose sodium.

In another embodiment, the active ingredient of component a) is selected from the group consisting of valproic sodium acid, a pharmaceutically acceptable salt or ester of valproic acid, divalproex sodium, valpromide,
N-(2-Propylpentanoyl)glycinamide,
N-(2-propylpentanoyl)glycine-N'-methylamide,
N-(2-propylpentanoyl)glycine-N'-butylamide,
N-(2-propylpentanoyl)leucinamide,
N-(2-propylpentanoyl)alanine-N'-benzylamide,
N-(2-propylpentanoyl)alapinamide,
N-(2-propylpentanoyl)-2-phenylglycinamide,
N-(2-propylpentanoyl)threoninamide,
N-(2-propylpentanoyl)glycine-N',N'-dimethylamide,
N-(2-propylpent-2-enoyl)glycinamide,
N-(2-propylpent-2-enoyl)alaninamide, and
N-(2-propylpent-2-enoyl)glycine-N'-methylamide.

The subject invention also provides an immediate release tablet comprising the following components:

a) a uniform admixture of:
   (i) N-(2-Propylpentanoyl)glycinamide; and
   (ii) a hydroxypropyl cellulose; and
b) a disintegrant.

In one embodiment, the uniform admixture of component a) further comprises a filler, and the tablet further comprises a filler and a lubricant as additional components.

In one embodiment, the filler of component a) is a microcrystalline cellulose, lactose, a starch, or a combination of two or more of the foregoing.

In a further embodiment, the filler of component a) is a microcrystalline cellulose.

In another embodiment, the additional filler is a microcrystalline cellulose, lactose, a starch, or a combination of two or more of the foregoing.

In a further embodiment, the additional filler is a microcrystalline cellulose.

In another embodiment, the additional filler is lactose.

In another embodiment, the lubricant is magnesium stearate, sodium stearyl fumarate, hydrogenated castor oil, hydrogenated soybean oil, polyethylene glycol or a combination of two or more of the foregoing.

In a further embodiment, the lubricant is magnesium stearate.

In a further embodiment, the lubricant is sodium stearyl fumarate.

In a further embodiment, the disintegrant of component b) is croscarmellose sodium, sodium starch glycolate or a combination thereof.

In another embodiment, the disintegrant of component b) is croscarmellose sodium.

In another embodiment, the tablet comprises the following components:

a) a uniform admixture of

from 50 mg/tablet to 1000 mg/tablet N-(2-Propylpentanoyl)glycinamide; and

from 5 mg/tablet to 150 mg/tablet hydroxypropyl cellulose; and

b) from 1 mg/tablet to 100 mg/tablet croscarmellose sodium.

In another embodiment, component a) further comprises from 1 mg/tablet to 300 mg/tablet microcrystalline cellulose as an additional component.

In another embodiment, component b) further comprises

from 5 mg/tablet to 500 mg/tablet filler; and

from 0.1 mg/tablet to 20 mg/tablet lubricant.

In another embodiment, the tablet comprises the following components:

a) a uniform admixture of

from 250 mg/tablet to 500 mg/tablet N-(2-Propylpentanoyl)glycinamide; and

from 25 mg/tablet to 50 mg/tablet hydroxypropyl cellulose; and

b) from 40 mg/tablet to 60 mg/tablet croscarmellose sodium.

In another embodiment, component a) further comprises from 50 mg/tablet to 100 mg/tablet microcrystalline cellulose as an additional component.

In another embodiment, component b) further comprises
from 100 mg/tablet to 500 mg/tablet filler; and
from 2 mg/tablet to 20 mg/tablet lubricant.

In a further embodiment, component b) comprises
from 5 mg/tablet to 20 mg/tablet lubricant.

In a further embodiment, component b) comprises
from 10 mg/tablet to 20 mg/tablet.

In a further embodiment, component b) comprises
from 15 mg/tablet to 20 mg/tablet.

In a further embodiment, component b) comprises
from 150 mg/tablet to 500 mg/tablet filler.

In a further embodiment, component b) comprises
from 200 mg/tablet to 500 mg/tablet filler.

In a further embodiment, component b) comprises
from 250 mg/tablet to 500 mg/tablet filler.

In a further embodiment, component b) comprises
from 300 mg/tablet to 500 mg/tablet filler.

In a further embodiment, component b) comprises
from 350 mg/tablet to 500 mg/tablet filler.

In a further embodiment, component b) comprises
from 400 mg/tablet to 500 mg/tablet filler.

In a further embodiment, component b) comprises from 450 mg/tablet to 500 mg/tablet filler.

In a further embodiment, component b) comprises any combination of the aforementioned ranges of filler and lubricant.

In another embodiment,

the additional filler is lactose, microcrystalline cellulose, mannitol or a combination of two or more of the foregoing; and

the lubricant is magnesium stearate or sodium stearyl fumarate or a combination thereof.

In another embodiment, the tablet comprises the following components:

a) a uniform admixture of
500 mg/tablet N-(2-Propylpentanoyl) glycinamide;
50 mg/tablet hydroxypropyl cellulose; and
100 mg/tablet a microcrystalline cellulose, and
b) 55 mg/tablet croscarmellose sodium;
145 mg/tablet lactose; and
6 mg/tablet magnesium stearate.

In another embodiment, the tablet comprises the following components:

a) a uniform admixture of
500 mg/tablet N-(2-Propylpentanoyl) glycinamide;
50 mg/tablet hydroxypropyl cellulose; and
100 mg/tablet a microcrystalline cellulose, and
b) 50 mg/tablet croscarmellose sodium;
145 mg/tablet lactose; and
6 mg/tablet magnesium stearate.

In another embodiment, the tablet comprises

a) a uniform admixture of:
250 mg/tablet N-(2-Propylpentanoyl) glycinamide;
25 mg/tablet hydroxypropyl cellulose; and
50 mg/tablet microcrystalline cellulose;

b) 450 mg/tablet microcrystalline cellulose;
50 mg/tablet croscarmellose sodium; and
6 mg/tablet magnesium stearate.

The subject invention also provides a method of treating neuropathic pain in a subject in need of such treatment comprising administering to the subject a therapeutically effective dose of any of the solid dosage forms or tablets of the invention in order to thereby treat the neuropathic pain in the subject.

The subject invention also provides a method of treating a headache disorder in a subject in need of such treatment comprising administering to the subject a therapeutically effective dose of any of the solid dosage forms or tablets of the invention in order to thereby treat the headache disorder in the subject.

The subject invention also provides a method of treating epilepsy in a subject in need of such treatment comprising administering to the subject a therapeutically effective dose of any of the solid dosage forms or tablets of the invention in order to thereby treat epilepsy in the subject.

The subject invention also provides a method of controlling seizures in a subject suffering from epilepsy comprising administering to the subject a therapeutically effective dose of any of the solid dosage forms or tablets of the

invention in order to thereby control the seizures in the subject.

The subject invention also provides a method of treating pain in a subject in need of such treatment comprising administering to the subject a therapeutically effective dose of any of the tablets of the invention in order to thereby treat pain in the subject.

The subject invention also provides a method of pain prophylaxis in a subject in need of such treatment comprising administering to the subject a prophylactic dose of any of the tablets of the invention in order to thereby effect pain prophylaxis in the subject.

The subject invention also provides a method of treating mania in bipolar disorder in a subject in need of such treatment comprising administering to the subject a therapeutically effective dose of any of the tablets of the invention in order to thereby treat mania in bipolar disorder in the subject.

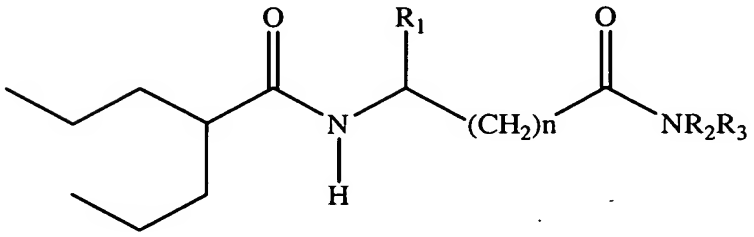
The subject invention also provides a method of attenuating bipolar mood swings in a subject suffering from bipolar disorder comprising administering to the subject a therapeutically effective dose of any of the solid dosage forms or tablets of the invention in order to thereby attenuate the bipolar mood swings in the subject.

The subject invention also provides a process for preparing the solid dosage form or tablet of the invention, comprising the steps of:

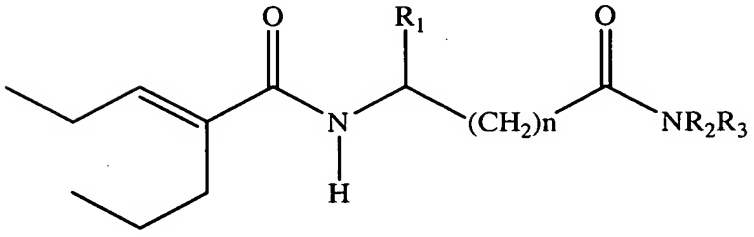
a) admixing predetermined amounts of

(i) an active ingredient selected from the group consisting of valproic sodium acid, a

pharmaceutically acceptable salt or ester of valproic acid, divalproex sodium, valpromide and a compound having the structure:



or



wherein R_1, R_2, and R_3 are independently the same or different and are hydrogen, a C_1-C_6 alkyl group, an aralkyl group, or an aryl group, and n is an integer which is greater than or equal to 0 and less than or equal to 3; and

(ii) a hydroxypropyl cellulose;

b) admixing the uniform mixture of step a) with a predetermined amount of a disintegrant; and

c) compressing the mixture of step b) to form the tablet.

In one embodiment, step b) further comprises admixing the uniform mixture with predetermined amounts of a filler and a lubricant.

In another embodiment, the filler of step b) is microcrystalline cellulose, anhydrous dicalcium phosphate, lactose or a combination of two or more of the foregoing.

In a further embodiment, the filler is lactose.

In a further embodiment, the filler is a microcrystalline cellulose.

In another embodiment, the lubricant is magnesium stearate or sodium stearyl fumarate or a combination thereof.

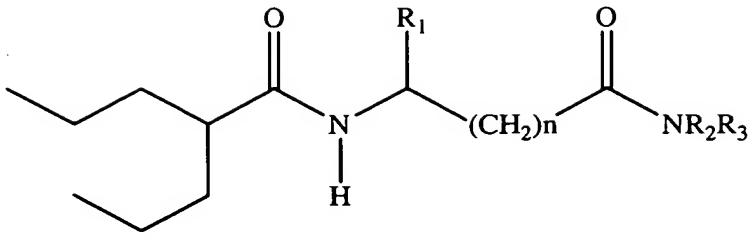
In a further embodiment, the lubricant is magnesium stearate.

In a further embodiment, the lubricant is sodium stearyl fumarate.

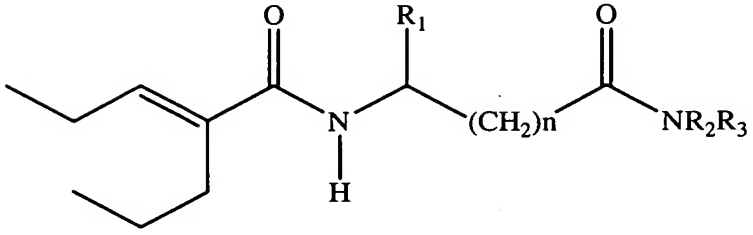
In another embodiment, the disintegrant of step b) is croscarmellose sodium, sodium starch glycolate or a combination thereof.

In a further embodiment, the disintegrant of step b) is croscarmellose sodium.

The subject invention also provides the use of an active ingredient selected from the group consisting of valproic sodium acid, a pharmaceutically acceptable salt or ester of valproic acid, divalproex sodium, valpromide and a compound having the structure:

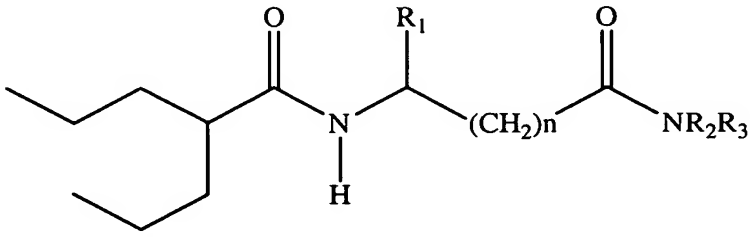


or

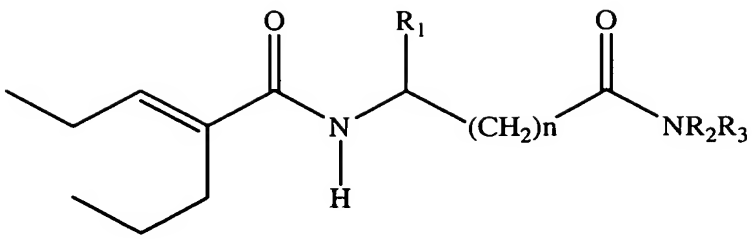


wherein R_1, R_2, and R_3 are independently the same or different and are hydrogen, a C_1-C_6 alkyl group, an aralkyl group, or an aryl group, and n is an integer which is greater than or equal to 0 and less than or equal to 3, for manufacturing any of the immediate release solid dosage forms or tablets of the invention for use in treating a headache disorder in a subject.

The subject invention also provides the use of an active ingredient selected from the group consisting of valproic sodium acid, a pharmaceutically acceptable salt or ester of valproic acid, divalproex sodium, valpromide and a compound having the structure:

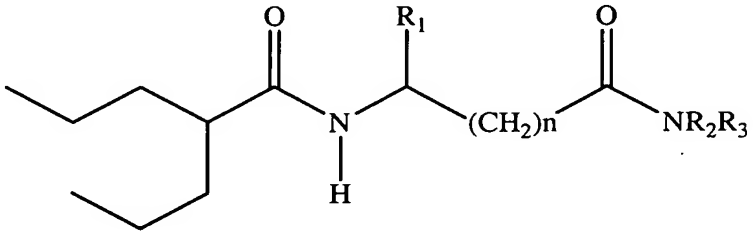


or

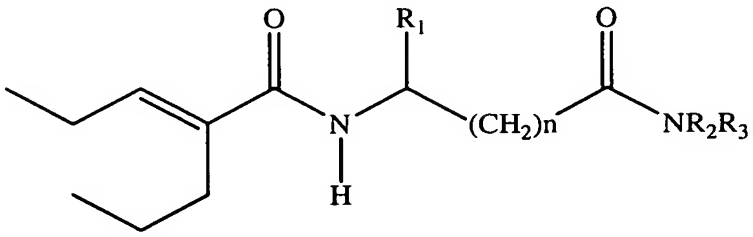


wherein R_1, R_2, and R_3 are independently the same or different and are hydrogen, a C_1-C_6 alkyl group, an aralkyl group, or an aryl group, and n is an integer which is greater than or equal to 0 and less than or equal to 3, for manufacturing any of the immediate release solid dosage forms or tablets of the invention for use in treating neuropathic pain in a subject.

The subject invention also provides the use of an active ingredient selected from the group consisting of valproic sodium acid, a pharmaceutically acceptable salt or ester of valproic acid, divalproex sodium, valpromide and a compound having the structure:

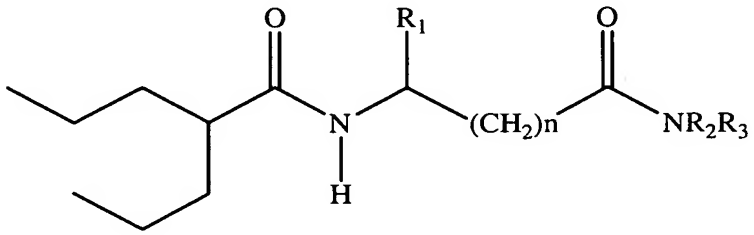


or

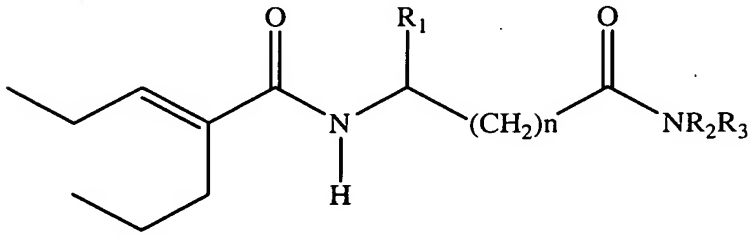


wherein R_1, R_2, and R_3 are independently the same or different and are hydrogen, a C_1-C_6 alkyl group, an aralkyl group, or an aryl group, and n is an integer which is greater than or equal to 0 and less than or equal to 3, for manufacturing any of the immediate release solid dosage forms or tablets of the invention for use in treating epilepsy in a subject.

The subject invention also provides the use of an active ingredient selected from the group consisting of valproic sodium acid, a pharmaceutically acceptable salt or ester of valproic acid, divalproex sodium, valpromide and a compound having the structure:



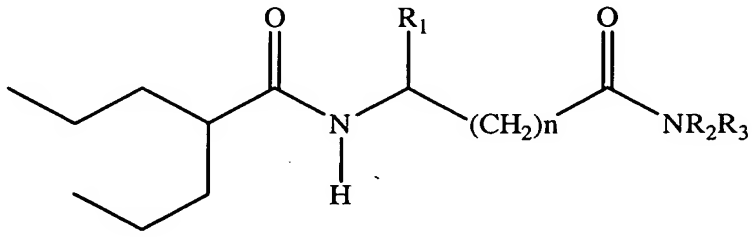
or



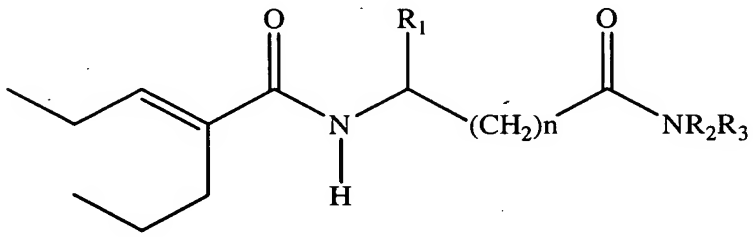
wherein R_1, R_2, and R_3 are independently the same or different and are hydrogen, a C_1-C_6 alkyl group, an aralkyl group, or an aryl group, and n is an integer which is greater than or equal to 0 and less than or equal to 3, for manufacturing any of the immediate release solid dosage forms or tablets of the invention

for use in controlling seizures in a subject suffering from epilepsy.

The subject invention also provides the use of an active ingredient selected from the group consisting of valproic sodium acid, a pharmaceutically acceptable salt or ester of valproic acid, divalproex sodium, valpromide and a compound having the structure:



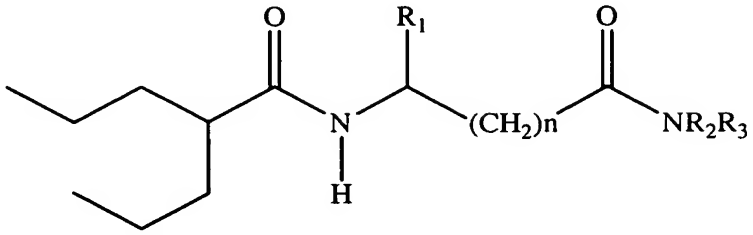
or



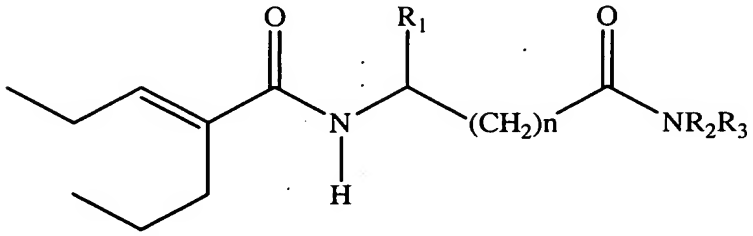
wherein R_1, R_2, and R_3 are independently the same or different and are hydrogen, a C_1-C_6 alkyl group, an aralkyl group, or an aryl group, and n is an integer which is greater than or equal to 0 and less than or equal to 3, for manufacturing any of the immediate release solid dosage forms or tablets of the invention for use in treating mania in bipolar disorder in a subject.

The subject invention also provides the use of an active ingredient selected from the group consisting of valproic sodium acid, a pharmaceutically acceptable salt or ester of

valproic acid, divalproex sodium, valpromide and a compound having the structure:

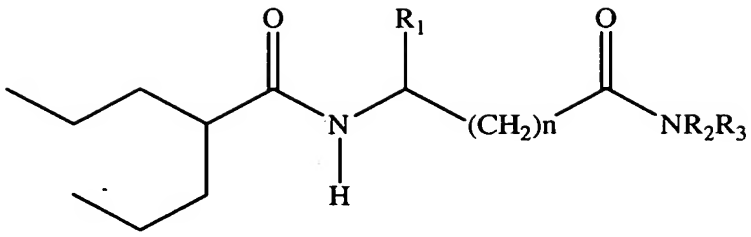


or

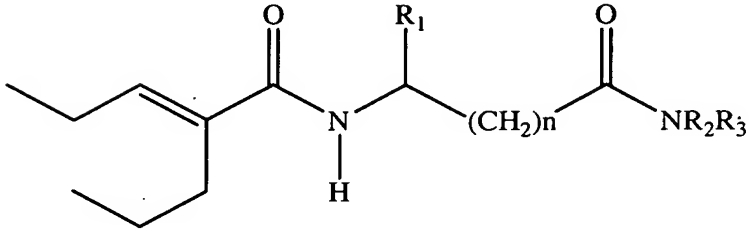


wherein R_1, R_2, and R_3 are independently the same or different and are hydrogen, a C_1-C_6 alkyl group, an aralkyl group, or an aryl group, and n is an integer which is greater than or equal to 0 and less than or equal to 3, for manufacturing any of the immediate release solid dosage forms or tablets of the invention for use in attenuating bipolar mood swings in a subject suffering from bipolar disorder.

The subject invention also provides the use of an active ingredient selected from the group consisting of valproic sodium acid, a pharmaceutically acceptable salt or ester of valproic acid, divalproex sodium, valpromide and a compound having the structure:

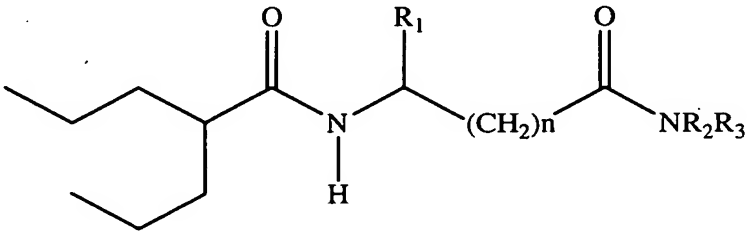


or

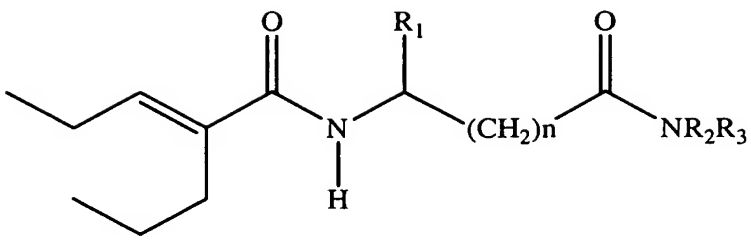


wherein R_1, R_2, and R_3 are independently the same or different and are hydrogen, a C_1-C_6 alkyl group, an aralkyl group, or an aryl group, and n is an integer which is greater than or equal to 0 and less than or equal to 3, for manufacturing any of the immediate release solid dosage forms or tablets of the invention for use in treating pain in a subject.

The subject invention also provides the use of an active ingredient selected from the group consisting of valproic sodium acid, a pharmaceutically acceptable salt or ester of valproic acid, divalproex sodium, valpromide and a compound having the structure:



or



wherein R_1, R_2, and R_3 are independently the same or different and are hydrogen, a C_1-C_6 alkyl group, an aralkyl group, or an aryl group, and n is an integer which is greater than or equal to 0 and less than or equal to 3, for manufacturing any of the immediate release solid dosage forms or tablets of the invention for use in effecting pain prophylaxis in a subject.

The subject invention also provides any of the above immediate release solid dosage forms or tablets for use in treating a headache disorder in a subject.

The subject invention also provides any of the above immediate release solid dosage forms or tablets for use in treating neuropathic pain in a subject.

The subject invention also provides any of the above immediate release solid dosage forms or tablets for use in treating epilepsy in a subject.

The subject invention also provides any of the above immediate release solid dosage forms or tablets for use in controlling seizures in a subject suffering from epilepsy.

The subject invention also provides any of the above immediate release solid dosage forms or tablets for use in treating mania in bipolar disorder in a subject.

The subject invention also provides any of the above immediate release solid dosage forms or tablets for use in

attenuating bipolar mood swings in a subject suffering from bipolar disorder.

The subject invention also provides any of the above immediate release solid dosage forms or tablets for use in treating pain in a subject.

The subject invention also provides any of the above immediate release solid dosage forms or tablets for use in effecting pain prophylaxis in a subject.

The subject invention provides an oral dosage of N-(2-propylpentanoyl)glycinamide in an immediate release form.

In one embodiment of the invention, the process for manufacturing the immediate release formulation of N-(2-propylpentanoyl)glycinamide comprises:

1. Preparing a granulate of N-(2-propylpentanoyl) glycinamide;
2. Mixing the granulate of step 1 with excipients; and
3. Compressing the mixture of step 2 to form an immediate release tablet of N-(2-propylpentanoyl) glycinamide.

In another embodiment, the process for manufacturing the immediate release formulation of N-(2-propylpentanoyl) glycinamide comprises:

1. Mixing the active material with excipients; and
2. Direct compression of the mixture of step 1.

As used herein, the phrase, "immediate release" indicates that the drug is allowed to dissolve in the gastrointestinal tract, with no intention of delaying or prolonging the dissolution or absorption of the drug (FDA Guideline for industry SUPAC-MR: modified release oral dosage forms CDER,

September, 1997). Immediate release formulations encompass, for example, rapid burst formulations.

Non-limiting examples of disintegrants used in the subject invention are kaolin starch, powdered sugar, sodium starch glycolate, crosscaramelose sodium, microcrystalline cellulose, carboxymethyl cellulose and sodium alginate.

Non-limiting examples of a filler used in the subject invention (used for example for weight adjustment and for better compression) are corn starch, lactose, glucose, various natural gums, methylcellulose, carboxymethylcellulose, microcrystalline cellulose, calcium phosphate, calcium carbonate, calcium sulfate kaolin, sodium chloride, powdered cellulose, sucrose, mannitol and starch.

Non-limiting examples of a binding agent used in the subject invention (used for example for the granulate) are alginic acid, acia, carbomer, carboxymethylcellulose sodium, dextrin, ethylcellulose, gelatin, guar gum, hydrogenated vegetable oil, hydroxyethylcellulose, hydroxypropylcellulose (e.g., Klucel®, Aqualon Division, Hercules Incorporated, Wilmington, Del.), hydroxypropylmethylcellulose, liquid glucose, magnesium aluminum silicate, maldodextrin, methylcellulose, polymethacrylates, povidone (polyvinylpyrrolidone), pregelatinized starch, sodium alginate, starch, and zein. In a preferred embodiment, the excipient used as a binding agent comprises a hydroxypropylcellulose.

In one embodiment, the excipient used as a binder is hydroxypropyl cellulose. In one embodiment, the hydroxypropyl cellulose has a particle size distribution such that about 85% of the hydroxypropyl cellulose passes through a 30 mesh screen. In another embodiment, the

hydroxypropyl cellulose has a particle size distribution such that about 99% of the hydroxypropyl cellulose passes through a 20 mesh screen. In another embodiment, the hydroxypropyl cellulose has a pH of 5.0-7.5 in water solution. In one embodiment, the hydroxypropyl cellulose has an average molecular weight of 1,150,000. In one embodiment, the hydroxypropyl cellulose has an average molecular weight of 850,000. In one embodiment, the hydroxypropyl cellulose has an average molecular weight of 370,000. In one embodiment, the hydroxypropyl cellulose has an average molecular weight of 140,000. In one embodiment, the hydroxypropyl cellulose has an average molecular weight of 95,000. In one embodiment, the hydroxypropyl cellulose has an average molecular weight of 80,000. In one embodiment, the hydroxypropyl cellulose has a viscosity of 1,500-3,000 cps at a concentration of 1% by weight in water at 25°C. In one embodiment, the hydroxypropyl cellulose has a viscosity of 4,000-6,500 cps at a concentration of 2% by weight in water at 25°C. In one embodiment, the hydroxypropyl cellulose has a viscosity of 150-400 cps at a concentration of 2% by weight in water at 25°C. In one embodiment, the hydroxypropyl cellulose has a viscosity of 150-400 cps at a concentration of 5% by weight in water at 25°C. In one embodiment, the hydroxypropyl cellulose has a viscosity of 75-150 cps at a concentration of 5% by weight in water at 25°C. In one embodiment, the hydroxypropyl cellulose has a viscosity of 200-600 cps at a concentration of 10% by weight in water at 25°C. In one embodiment, the hydroxypropyl cellulose has a viscosity of 75-150 cps at a concentration of 5% by weight in water at 25°C. In one embodiment, the hydroxypropyl cellulose has a viscosity of 300-600 cps at a concentration of 10% by weight in water at 25°C.

In one embodiment, the excipient used as a filler is a microcrystalline cellulose. In an added embodiment, the microcrystalline cellulose has an average particle size between about 20 and about 200 microns. In an added embodiment, the microcrystalline cellulose has an average particle size between about 50 and about 90 microns.

Details of general formulation procedures and information on additional excipients may be found in Remington: The Science and Practice of Pharmacy, 20th Edition.

This invention will be better understood from the Experimental Details which follow.

Experimental details:

Two clinical trials, single and multiple dose, were performed in healthy male volunteers by administration of the N-(2-propylpentanoyl)glycinamide drug product in capsules.

In a subsequent clinical trial, the drug product was administered in caplet shaped tablets. In order to confirm that the capsule and tablet forms of the drug were equivalent, the properties of the two dosage forms were studied. The results of the study are presented below.

Example 1: Comparison of capsule and caplet formulations

The drug product used in this study was manufactured in two strengths. Each caplet contained 250mg or 500mg of N-(2-propylpentanoyl)glycinamide. Each capsule contained 250 mg or 50 mg of N-(2-propylpentanoyl)glycinamide.

Table 1: Composition of N-(2-propylpentanoyl)glycinamide capsule (250mg and 50mg)

Ingredients	N-(2-propylpentanoyl) glycinamide Capsule 250mg	N-(2-propylpentanoyl) glycinamide Capsule 50mg
N-(2-propylpentanoyl) glycinamide	250.0 mg	50.0 mg
Lactose Spray Dried	67.5 mg	399.5 mg
Aerosil 200*	2.5 mg	0.5 mg

* Colloidal silicon dioxide NF

Table 2: Composition of N-(2-propylpentanoyl)glycinamide caplets (250mg)

Ingredients	mg per caplet	Function	Reference to standards
N-(2-propylpentanoyl) glycinamide	250	Active Ingredient	Teva Ref. standard
Povidone USP (PVP K-30)	30	Binder	USB/BP
Sodium Starch Glycolate NF	25	Disintegrate	NF/BP
Lactose Monohydrate (200 Mesh)	123.5	Bulking agent	NF/BP
Starch NF	50	Binder	NF/BP
Glycerin USP	2.5	Humectant	USP
Avicel PH 102 (Microcorystalline Cellulose	246.5	Diluent	NF/Ph.Eur/Jp
Croscarmellose Sodium (Ac-Di-Sol)	25	Disintegrate	NF
Magnesium Stearate	2.5	Lubricant	NF/BP
Purified Water		Moistener Removed during manufacture	USP

Table 3: Composition of N-(2-propylpentanoyl)glycinamide caplets (500mg)

Ingredients	mg per caplet	Function	Reference to standards
N-(2-propylpentanoyl) glycinamide	500	Active Ingredient	Teva Ref. standard
Povidone USP (PVP K-30)	30	Binder	USB/BP
Sodium Starch Glycolate NF	25	Disintegrant	NF/BP
Pregelatinized Starch (starch-STA-RX 1500 NF)	50	Binder	NF
Starch NF	50	Binder	NF/BP
Glycerin USP	2.5	Humectant	USP
Avicel PH 102 (Microcrystalline Cellulose)	70	Diluent	NF/Ph.Eur/Jp
Croscarmellose Sodium (Ac-Di-Sol)	25	Disintegrant	NF
Magnesium Stearate	2.5	Lubricant	NF/BP
Purified Water		Moistener Removed during manufacture	USP

Dissolution experiments using N-(2-propylpentanoyl) glycinamide capsules and N-(2-propylpentanoyl)glycinamide caplets (250mg and 500mg) exhibited a fast rate of dissolution. The percent dissolution after 10 minutes and after 45 minutes were as follows:

Table 3a: Percent dissolution

Dosage form	mg active per dosage form	Dissolution after 10 minutes	Dissolution after 45 minutes
Capsules	50 mg	Not available	96.9%
	250 mg	86.6%	99.0%
Caplets	250 mg	78.8%	94.8%
	500 mg	101.4%	93.7%

The two different dosage forms of N-(2-propylpentanoyl)glycinamide studied above (capsules and caplets) were found to be equivalent based on dissolution data of both formulations presented above.

Example 2: N-(2-propylpentanoyl)glycinamide granulate

In a further study, N-(2-propylpentanoyl)glycinamide was granulated with a binder solution and with several excipients. The granulate was then compressed into a tablet and the tablets were evaluated for their dissolution rates.

Table 4: Composition of the granulate

Excipient	Use	A	B
		Mg/tablet	
N-(2-propylpentanoyl) glycinamide	Active material	500	250
Microcrystalline Cellulose	Filler	100	50
Hydroxypropyl cellulose	Binder	50	25
Total		650	325

Table 5: Composition of the tablets

Excipient		A	B
	Use	Mg/tablet	
N-(2-propylpentanoyl) glycinamide granulate		650	325
Microcrystalline cellulose		-------	450
Lactose	Filler	145	------
Croscarmellose sodium	Disintegrant	50	50
Magnesium Stearate	Lubricant	6.0	6.0

The tablets were prepared by mixing the granulate with several excipients (table 5). Each formulation was tested in a dissolution test using 900 ml purified water, 37°C, in App. 2 US Pharmacopoeia (USP), at 75 RPM.

Table 6: Dissolution of N-(2-propylpentanoyl)glycinamide tablets

Formula	A	B
Time(min.)	% Dissolution	
10	97	94
15	98	96
30	98	96
45	98	96

As can be seen the two different dosages (A and B) of N-(2-propylpentanoyl)glycinamide gave the same dissolution profile. The two dosages also exhibited good compression properties.

Example 3: Effect of variation in the composition of the tablet

Table 7: Composition of the tablets

FORMULA	USE	C	D
PART I		Mg/tablet	
N-(2-propylpentanoyl) glycinamide		250	500
Sodium Starch Glycolate NF	Disintegrant	30	30
Starch STA-RX 1500	Disintegrant	120	65
Starch NF	Filler/Binder	40	20
Avicel PH 101 (Microcrystalline cellulose)	Filler	155	-
PART II			
Klucel LF	Binder	40	30
PART III			
Avicel PH 102 (Microcrystalline cellulose)	Filler	100	90
AC-DI-SOL (Croscarmellose sodium)	Disintegrant	30	30
Magnesium Stearate	Lubricant	3	3

Formulations C and D, each containing different excipients than formulations A and B were tested in order to determine the effect of varying the composition of the granulate and tablet matrix on the dissolution rate and on the physical properties of the manufactured tablets.

Each formulation was tested in a dissolution test using 900 ml purified water 37°C, in App.2 US Pharmacopoeia (USP).

Table 8: Dissolution of tablets

Formula	C	D
Time(min.)	% Dissolution	
10	98	94
15	101	94
30	101	95
45	101	95

As shown above, the dissolution profile was found to be dependent upon the specific formulations. However, the physical compression properties of formulations A and B were found to be much better than formulations C and D.

Example 4: Effect of the amount loss on drying (L.O.D.) in the granulate

Table 9:

Formula	**USE**	**E**	**F**	**G**	**GG**
		Mg/tablet			
N-(2-propylpentanoyl) glycinamide granulate		650	650	650	650
Avicel PH 102 (Microcrystalline cellulose)	Filler	125	125	125	125
AC-DI-SOL (Croscarmellose sodium)	Disintegrant	50	50	50	50
Magnesium Stearate	Lubricant	6.0	6.0	6.0	6.0
L.O.D.		1.0	1.6	2.0	3.0

Table 10: Dissolution of formulations

Formula	E	F	G	GG
Time(min.)	% Dissolution			
10	84	90	80	91
15	101	98	91	104
30	103	100	99	108
45	103	100	102	108

As can be seen, the dissolution rate did not change due to changes in the amounts of the L.O.D. The physical properties also remained the same and the tablets were compressible in this range of the L.O.D.

Example 5: Effect of the binder in the granulate

Table 11:

Formula	Use	H	I
N-(2-propylpentanoyl) glycinamide		500	500
Sodium Starch Glycolate NF	Disintegrant	25	30
Starch STA-RX 1500	Disintegrant	50	65
Binder Excipients			
Starch NF	Filler/Binder	25	20
Klucel LF	Binder	-----	30
Starch NF	Filler/Binder	25	------
Glycerin USP		2.5	------
PVP-K-30 (Povidone USP)	Binder	30	------

Table 12: Dissolution of formulation

Formula	H	I
Time(min.)	% Dissolution	
10	96	100
15	96	103
30	97	103
45	97	103

As shown above, changing the type of binder did not change the dissolution rate. However, it had an effect on the granulate's physical properties. In particular, compression was more readily accomplished when Klucel was used as a binder.

Example 6: Effect of Lubricant type on dissolution rate

Table 13a:

Formula	USE	J	K
N-(2-propylpentanoyl) glycinamide granulate		650	650
LACTOSE	Filler	145	145
AC-DI-SOL (croscarmellose sodium)	Disintegrant	50	50
Magnesium Stearate	Lubricant	----	6.0
Pruv	Lubricant	6.0	----

Table 13b:

Formula	J	K
Time (min)	% dissolution	
10	86	97
15	98	98
30	97	98
45	97	98

Changing the type of the lubricant did not change the dissolution rate. However, the type of lubricant did have an effect on the physical properties of the tablets. Compression was more easily accomplished when Pruv was used as the lubricant.

Example 7: Effect of Lubricant amount on dissolution rate

Table 14: Lower dosage tablets (325 mg of granulate/tablet)

Formula	USE	L	M	N
N-(2-propylpentanoyl) glycinamide granulate		325	325	325
avicel PH 102 (microcrystalline cellulose)	Filler	450	450	450
AC-DI-SOL (croscarmellose sodium)	Disintegrant	50	50	50
Magnesium Stearate	Lubricant	4.5	6.0	7.5

Changing the amount of the lubricant did not change the dissolution rate of the lower dosage tablets.

Table 15: Higher dosage tablets (650 mg of granulate/tablet)

Formula	USE	LL	MM	NN
N-(2-propylpentanoyl) glycinamide granulate		650	650	650
Lactose	Filler	145	145	145
AC-DI-SOL (croscarmellose sodium)	Disintegrant	50	50	50
Magnesium Stearate	Lubricant	3	6	9

Table 16: Dissolution of formulation

Formula	LL	MM	NN
Time(min)	% Dissolution		
10	84	97	91
15	97	98	99
30	100	98	100
45	101	98	100

As shown above, changing the amount of the lubricant did not change the dissolution rate of the higher dosage tablets.

Example 8: Effect of the filler material on the tabletting process

Table 17:

Formula	USE	O	P	Q
N-(2-propylpentanoyl) glycinamide granulate		650	650	650
avicel PH 102 (microcrystalline cellulose)	Filler	125	------	-----
Mannitol	Filler	----------	125	--------
Lactose	Filler	-------	-------	145
AC-DI-SOL (croscarmellose sodium)	Disintegrant	50	50	50
Magnesium Stearate	Lubricant	6.0	6.0	6.0

Table 18: Dissolution of formulations

Formula	O	Q
Time(min.)	% Dissolution	
10	80	97
15	91	98
30	99	98
45	102	98

As shown above, changing the amount of the filler did not change the dissolution rate. However, changing the amount of filler had an effect on the physical properties of the

compression. In particular, formulations which used lactose S.D. as the filler were more easily compressed.

Example 9: Effect of the amount of disintegrate on the dissolution rate

Table 19:

Formula	USE	R	S	RR	SS
N-(2-propylpentanoyl) glycinamide granulate		325	325	650	650
Lactose	Filler	-------	------	145	145
Avicel PH 102 (Microcrystalline cellulose)	Filler	450	450	-----	-----
AC-DI-SOL (Croscarmellose sodium)	Disintegrant	50	40	50	45
Magnesium Stearate	Lubricant	6.0	6.0	6.0	6.0

Table 20: Dissolution of formulation

Formula	RR	SS
Time(min.)	% Dissolution	
10	97	66
15	98	91
30	98	100
45	98	100

As shown above, the amount of disintegrant significantly effects the dissolution rate of the formulation for the

first 10 minutes. However, After 15 minutes, this effect is no longer discernible.

Example 10: Effect of the milling of the granulate on dissolution rate

Table 21:

Formula	USE	V (Screen of 0.8mm)	W (Screen of 1.0mm)	X (Screen of 1.2mm)
N-(2-propylpentanoyl) glycinamide granulate		650	650	650
Lactose	Filler	145	145	145
AC-DI-SOL (croscarmellose sodium)	Disintegrant	50	50	50
Magnesium Stearate	Lubricant	6.0	6.0	6.0

Table 22: Dissolution of formulation

Formula	V	W	X
Time(min.)	% Dissolution		
10	92	100	93
15	103	105	102
30	104	106	105
45	105	106	105

As shown above, three granulates milled to different sizes gave similar dissolution rates.

5

Example 11: Effect of amount of filler on dissolution rate

Table 23:

Formula	USE	Y	Z	ZZ
		Mg/tablet		
N-(2-propylpentanoyl) glycinamide granulate		650	650	650
Lactose	Filler	145	140	150
AC-DI-SOL (croscarmellose sodium)	Disintegrant	50	50	50
Magnesium Stearate	Lubricant	6.0	6.0	6.0

Table 24: Dissolution of formulation

Formula	Y	Z	ZZ
Time(min.)	% Dissolution		
10	85	77	84
15	96	97	98
30	100	101	100
45	100	102	100

As illustrated above, the amount of filler had a negligible effect on the dissolution rate of the manufactured tablets.

Example 12

Plasma Concentration of N-(2-propylpentanoyl) glycinamide and of N-(2-propylpentanoyl) glycine after administration.

Formulation A was prepared as described in Example 2.

Three tablets of formulation A (3 X 500 mg active pharmaceutical ingredient) were simultaneously administered to each of 32 healthy male and female volunteers. Plasma concentrations of N-(2-propylpentanoyl) glycinamide and of a major metabolite, N-(2-propylpentanoyl) glycine of each of the volunteers were regularly analyzed at 0.25, 0.5, 0.75, 1.0, 1.5, 2, 4, 6, 8, 12, and 24 hours. The tablets were administered once while the volunteers were under fed conditions and once while the volunteers were fasting. Between the two administrations there was a seven-day washing out period.

The results of the trial were averaged and the mean plasma concentrations after administration to the fed and fasting groups are depicted in figures 1 and 2.

Discussion

The details of the manufacturing process of large dose tablets are a particularly important aspect of the present

invention. Large dose tablets present a unique set of problems as the dry mixture of active and inactive ingredients is often not easily compressible.

The present invention discloses a detailed manufacturing procedure which is designed to overcome the difficulties presented in manufacturing tablet or caplet dosages with large doses of the active ingredient. The satisfactory manufacture of large dose tablets or caplets is accomplished by including specific amounts of hydroxypropyl cellulose and other excipients in the tablet or caplet.

Although the plasma concentration results in Example 12 are all based on administration of a single, 1500 mg dose of N-(2-propylpentanoyl) glycinamide, a linear pharmacokinetic response is expected in patients upon administration of other doses. Such a response is expected based on the work of Blotnick et al. with related compounds in phase I studies in which the pharmacokinetics were shown to be dose-independent (Blotnick et al., "The Disposition of Valproyl Glycinamide and Valproyl Glycine in Rats" (1997) *Pharmaceutical Research* 14(7): 873-878).